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UTILITY PATENT APPLICATION TRANSMITTAL

(only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	ORT1316
First Named Inventor or Application Identifier	Michael E. Kafrissen
Express Mail Label No.	EL327259137US

APPLICATION ELEMENTS

See MPEP Chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. ☒ Fee Transmittal Form *(attached hereto in duplicate)*
2. ☒ Specification [Total Pages 33]
(Preferred arrangement set forth below)
- Descriptive Title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R&D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings *(if filed)*
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

3. ☐ Drawing(s)*(35 USC 113)* [Total Sheets]
4. Oath or Declaration
   a. ☐ Newly executed (original or copy)
   b. ☐ Unexecuted original
   c. ☒ Copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional check boxes 5 and 16)
   i. ☐ Deletion of Inventor(s)
   Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
5. ☒ Incorporation by Reference
(useable if Box 4c is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4c, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
a. ☐ Computer Readable Copy
b. ☐ Paper Copy (identical to computer copy)
c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)* ☐ Power of Attorney
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
14. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
15. ☐ Other:

JC922 U.S. PTO 09/677976 10/02/00

JC893 U.S. PTO 10/02/00

16. ☒ If a CONTINUING APPLICATION, *check appropriate box and supply the requisite information:*
Amend the specification by inserting before the first line: -- This is a ☒ Continuation ☐ Divisional ☐ Continuation-in-Part (CIP) of prior application No.: 09/292,027, filed April 16, 1999. --
17. For this divisional application, please cancel original Claims 1-20 and add Claim 21 of the prior application before calculating the filing fee.

18. CORRESPONDENCE ADDRESS

☐ Customer Number or Bar Code Label or ☒ Correspondence Address below

Name: Philip S. Johnson, Esq.
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19. TELEPHONE CONTACT

Please direct all telephone calls or telefaxes to Alan J. Morrison at:
Telephone: (732) 524-3592 Fax: (732) 524-2808

19. SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

NAME	Alan J. Morrison	Reg. No. 37399
SIGNATURE		
DATE	October 3, 2000	

FEE TRANSMITTAL	*Complete if Known*	
	Application Number	Not Yet Known
	Filing Date	Herewith
	First Named Inventor	Michael E. Kafrissen
	Group Art Unit	Not Yet Known
	Examiner Name	Not Yet Known
	Attorney Docket Number	ORT 1316

FEE CALCULATION

CLAIMS AS FILED

(1)	(2)	(3)	(4)	(5)
FOR:	NUMBER FILED	NUMBER EXTRA	RATE	BASIC FEE $760.00
TOTAL CLAIMS	1 - 20 =	0	x 18.00	$ 0.00
INDEPENDENT CLAIMS	- 3 =	-0-	x 78.00	$ 0.00
MULTIPLE DEPENDENT CLAIMS	☐	N/A	$260.00	
			TOTAL FEES	$ 760.00

METHOD OF PAYMENT

☒ Please charge Deposit Account No. 10-0750/1316/AJM in the amount of $760.00. Three copies of this sheet are enclosed.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required in connection with the filing of this communication, or credit any overpayment, to Account No. 10-0750/ORT1316/AJM. Three copies of this sheet are enclosed.

SUBMITTED BY:			*Complete (if applicable)*
Typed or Printed Name	Alan J. Morrison		Reg. No. 37,399
Signature		Date: Oct. 3, 2000	**Deposit Account No. 10-0750**

DOCKET NO. ORT 1316

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant: Michael E. Kafrissen, Godfrey P. Oakley

For : PHARMACEUTICAL METHODS OF DELIVERING FOLIC ACID

Express Mail Certificate

"Express Mail" mailing number: EL327259137US

Date of Deposit: October 3, 2000

I hereby certify that this complete continuation application, including specification pages, claims and abstract, is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Alwin Haywood
(Typed or printed name of person mailing paper or fee)

Alwin M. Haywood
(Signature of person mailing paper or fee)

DKT NO. ORT-1316

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Michael E. Kafrissen and Godfrey P. Oakley

Serial No.: Not yet known

Filed : Herewith

For : PHARMACEUTICAL METHODS OF DELIVERING FOLIC ACID

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

This application is a continuation of parent application U.S. Serial No. 09/292,027, filed April 16, 1999. During prosecution of the parent application, applicants canceled claims 10 and 11 without prejudice in order to expedite allowance of the remaining claims. The parent application was allowed and is still pending, and applicants are filing this continuation application in order to pursue certain subject matter of canceled claims 10 and 11.

Please amend the subject application as follows:

In the Title:

Please delete "FOLIC ACID-CONTAINING PHARMACEUTICAL COMPOSITIONS, AND RELATED METHODS AND DELIVERY SYSTEMS", and insert --PHARMACEUTICAL METHODS OF DELIVERING FOLIC ACID--.

In the Specification:

At page 1, before the first sentence, please insert --This application is a continuation of U.S. Serial No. 09/292,027, filed April 16, 1999, which is a non-provisional of U.S. Serial No. 60/082,068, filed April 17, 1998, the contents of which are hereby incorporated by reference.--

In the Claims:

Please cancel claims 1-20 without prejudice to applicants' right to pursue the subject matter thereof in a later filed application.

Please add new claim 21 as follows:

21. (New) A method of administering folic acid to a subject for whom an oral contraceptive is indicated for preventing pregnancy, which comprises administering to the subject a pharmaceutical composition, wherein

(a) the pharmaceutical composition comprises an oral contraceptive for preventing pregnancy in a subject, and folic acid in an amount sufficient to treat or prevent cervical displasia or cervical carcinoma which (i) afflicts subjects for whom the oral contraceptive is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration, and

(b) the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, cervical displasia or cervical carcinoma at a

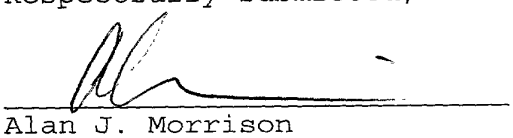
higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

REMARKS

Claims 1-20 are pending. Applicants have canceled claims 1-20, and added new claim 21. Claim 21 is now being prosecuted.

Support for new claim 21 can be found at, *inter alia*, page 10, lines 8-24 and page 11, lines 5-12 of the specification. Thus, applicants maintain that the amendments to the application raise no issue of new matter.

Respectfully submitted,



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October 3, 2000

FOLIC ACID-CONTAINING PHARMACEUTICAL COMPOSITIONS, AND RELATED METHODS AND DELIVERY SYSTEMS

Throughout this application, various publications are cited. The disclosure of these publications is hereby incorporated by reference into this application to describe more fully the state of the art to which this invention pertains.

Field of the Invention

This invention relates to compositions and methods for delivering folic acid to subjects afflicted with, or at an increased risk of becoming afflicted with, a folic acid-treatable disorder. The folic acid is incorporated into a chronically administered pharmaceutical composition intended for treating or preventing a condition different than the folic acid-treatable disorder.

Background of the Invention

Folic Acid Generally

Folic acid is a vitamin. It plays a crucial role in DNA synthesis, and in hematopoiesis (although the details of this role remain undefined). Folic acid is involved, for example, in single carbon transfers (such as those required for purine and pyrimidine metabolism), and in the re-methylation of homocysteine to methionine.

Folic acid is available, primarily as the polyglutamate, from dietary sources such as whole grains, mushrooms, vegetables, red meat, fish and legumes. Supplementation, however, is provided in the form of the monoglutamate (pteroglutamic acid). Folic acid is absorbed primarily in the proximal small bowel, is highly protein-bound, and is stored in the liver. Almost no unchanged folic acid appears in the urine under normal circumstances, unless excess is provided.

Minimum requirements of folic acid are in the range of 50 µg/day, and increase 3 to 6 times during pregnancy and/or lactation. The U.S. recommended daily allowance for pregnant women is 400 µg/day, and the average pharmacological replacement dose is between 1 and 5 mg/day. Most prenatal vitamins contain 1 mg of folic acid.

The total body store of folic acid is about 5 mg. When a folic acid-deficient patient is treated, reversal of the deficiency begins rapidly (reticulocytosis within 4 days) and resolves within 2 months. If folic acid is administered at a rate of only 50 µg day, assuming no dietary or other intake, signs of folic acid deficiency are manifest after an approximately 3 month lag time. In cases of increased bodily folic acid requirements, such as pregnancy or lactation, this time frame is shortened to 2 to 4 weeks. Fortunately, folic acid supplementation in otherwise healthy young women who have such increased folic acid needs is an accepted practice.

Folic acid has not been reported to cause adverse effects when administered in reasonable, pharmacological doses. The only reported adverse reaction for folic acid

is a decreased level of plasma zinc in the case of prolonged high-dose administration.

Oral Contraceptives and Folic Acid

In pregnant women, correction of low folic acid levels takes at least two months, and reserves can last as little as a few weeks. According to a public health service recommendation, all women who can become pregnant should consume 400 μg/day of folic acid to reduce the risk of birth defects (MMWR Morb Mortal Wkly Rep 1992; 41(RR-14):1-7). Supplementation immediately before discontinuing oral contraceptive use or immediately after positive pregnancy test results may be insufficient to optimally protect the developing fetus.

In addition, multiple studies of women taking oral contraceptives show decreased folic acid levels relative to negative controls. Postulated mechanisms reported for this phenomenon include decreased absorption of polyglutamates, increased excretion of folic acids, increased production of folic acid-binding proteins, and induction of folic acid-dependent hepatic microsomal enzymes.

Decreases of folic acid levels among oral contraceptive users pose an additional risk for such users who become pregnant within three to six months following discontinuation of use.

Disorders and Folic Acid

Numerous disorders can result from insufficient intake of folic acid. Enhanced effects of risk factors for cervical dysplasia (e.g. HPV infection) have been linked to decreased folic acid levels. Sub-optimal body stores of folic acid, as measured by red cell folic acid concentrations, may amplify oncogenic risk. Locally diminished folic acid stores, for example, in cervical tissue, may be a result of oral contraceptive use and are responsible for the dysplastic process. Finally, decreased folic acid levels early in pregnancy are associated with increased birth defects, primarily neural tube defects ("NTD's"). Indeed, randomized control trials of vitamin supplements containing folic acid have shown a dramatic reduction of the incidence of spina bifida and anencephaly.

Administering folic acid can reduce the onset of disorders such as cardiovascular disease and cervical dysplasia. For example, most clinical trials show that high folic acid doses (up to 10 mg/day) have a prophylactic, although not therapeutic, effect against cervical dysplasia (Butterworth, C.E., et al., JAMA (1992) 267(4):528-533; Butterworth C.E., et al., Am J Obstet Gynecol (1992) 166:803-809; Potischman, N. and Brinton, L.A., Cancer Causes and Control (1996) 7:113-126).

As for certain cardiovascular disorders, results from numerous studies indicate that doses of folic acid (1-5 mg/day) reduce elevated levels of homocysteine which can cause such disorders (Boushey, C.J., et al., JAMA (1995) 274:1049-1057); Landgren, F., et al., J Intern Med

(1995) 237:381-388). A single study by Guttormsen (Guttormsen, A.B., et al., J Clin Invest (1996) 98:2174-2183) demonstrated that low-dose folic acid supplementation (200 μg/day) reduces elevated plasma homocysteine levels in patients with intermediate hyperhomocysteinemia (> 40 μmol/L). This reduction is influenced, in part, by the initial causes of hyperhomocysteinemia, i.e., genetic mutation, dietary deficiency and concurrent disease.

Summary of the Invention

This invention provides a pharmaceutical composition comprising (a) an oral contraceptive for preventing pregnancy in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the oral contraceptive is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention also provides a pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a menopausal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention further provides a pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a hypogonadal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom an oral contraceptive is indicated for preventing pregnancy, which comprises administering to the subject the instant

pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a menopausal condition, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a hypogonadal condition, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

Finally, this invention provides a drug delivery system comprising a pharmaceutical package containing a plurality of dosage units, adapted for successive daily administration, wherein each dosage unit comprises at least one of the instant pharmaceutical compositions.

Detailed Description of the Invention

Definitions

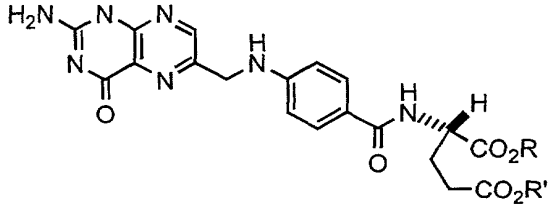
In this invention, certain terms are used which shall have the meanings set forth as follows.

"Androgen-related compound" ("ARC") shall mean a compound which displays an end organ androgen effect. ARC's are exemplified in the Examples below.

"Chronic administration" shall mean administration which occurs either at regular intervals (e.g., daily oral dosage) or continuously (e.g. transdermal delivery for several days) over at least a single time period (e.g., three weeks). The chronic administration can optionally occur over a plurality of time periods.

"Estrogen-related compound" ("ERC") shall mean a compound which displays an end organ estrogen effect. ERC's are exemplified in the Examples below.

"Folic acid" shall mean the compound having the following structure, where R and R' are both H, as well as pharmaceutically acceptable salts and derivatives thereof:



Pharmaceutically acceptable salts are well known in the art and include, without limitation, Na^+, K^+, Mg^{++} and

various amines (Int'l. J. Pharm. (1986) 33:201-217). Pharmaceutically acceptable derivatives are also well known in the art and include, without limitation, esters. Such derivatives are exemplified below.

"Menopausal condition" shall mean a condition that is either a peri-menopausal condition or a post-menopausal condition.

"Menopausal woman" shall mean a woman having an age at which menopause or its onset normally occurs.

"Peri-menopausal condition" shall mean a condition which (i) occurs either during menopausal onset, or prior thereto at a time when menopausal onset normally occurs, and (ii) either is caused by menopausal onset or has a greater than random coincidence therewith. Peri-menopausal conditions include, for example, hot flashes and reduction of bone mass.

"Post-menopausal condition" shall mean a condition which (i) occurs after menopausal onset, and (ii) either is caused by menopause or has a greater than random coincidence therewith. Post-menopausal conditions include, for example, vasomotor symptoms, osteopenia, osteoporosis, cardiovascular disease and cognitive dysfunction.

"Progestin-related compound" ("PRC") shall mean a compound which displays an end organ progestin effect. PRC's are exemplified in the Examples below.

"Subject" shall any animal, such as a primate, mouse, rat, guinea pig or rabbit. In the preferred embodiment, the subject is a human.

Embodiments of the Invention

This invention provides a pharmaceutical composition comprising (a) an oral contraceptive for preventing pregnancy in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the oral contraceptive is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention also provides a method of administering folic acid to a subject for whom an oral contraceptive is indicated for preventing pregnancy, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

Oral contraceptives are widely available commercially, and classifications thereof include, without limitation, progestin only, fixed dose, and phasics. Oral contraceptives routinely contain one or more estrogen-related compounds and progestin-related compounds. Such contraceptives are preferred in this invention and are listed extensively, along with their respective hormone ingredients, in the IPPF Directory of Hormonal Contraceptives. For the purpose of

illustration, selected oral contraceptives and their respective hormone ingredients are listed in the Examples below.

In this embodiment, the disorder can be any folic acid-treatable condition with which pregnant women are afflicted, or to which they are predisposed to become afflicted, at a higher-than-normal incidence. In the preferred embodiment, the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

This invention also provides a pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a menopausal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a menopausal condition, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

The menopausal condition can be a peri-menopausal condition or, alternatively, a post-menopausal condition. Hormonal replacement compositions are widely available commercially, and routinely contain estrogen-related compounds, progestin-related compounds, androgen-related compounds, and others. Such compositions are preferred in this invention and are listed extensively, along with their respective hormone ingredients, in Sturdee, D.W., et al. (Br J Obstet Gynecol (1997) 104:109-115). By way of example, selected hormone replacement compositions and their respective hormone ingredients are listed in the Examples below.

In this embodiment, the disorder can be any folic acid-treatable condition with which menopausal women are afflicted, or to which they are predisposed to become afflicted, at a higher-than-normal incidence. In the preferred embodiment, the disorder is selected from the group consisting of cervical dysplasia, cervical carcinoma and a cardiovascular disorder.

This invention also provides a pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a hypogonadal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or

preventing a hypogonadal condition, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

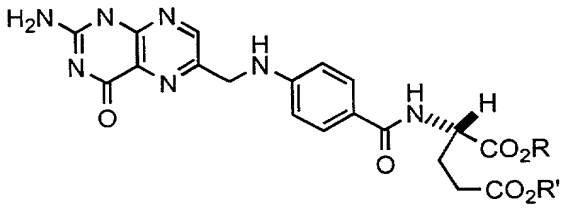
Hormone replacement compositions for hypogonadal conditions routinely contain androgen-related compounds (for male subjects) and estrogen- and progestin-related compounds (for female subjects). Hypogonadal conditions include, by way of example, menopause (with or without reduced libido), Klinefelter's syndrome, and post-orchectomy status. When the subject is female, the disorder can be selected, for example, from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder. When the subject is male, the disorder can be, for example, a cardiovascular disorder.

In this invention, administering the instant pharmaceutical compositions can be effected or performed using any of the various methods and delivery systems known to those skilled in the art. The administering can be performed, for example, intravenously, orally, via implant, transmucosally, transdermally, intramuscularly, and subcutaneously. In addition, the instant pharmaceutical compositions ideally contain one or more routinely used pharmaceutically acceptable carriers. Such carriers are well known to those skilled in the art. The following delivery systems, which employ a number of routinely used carriers, are only representative of the

many embodiments envisioned for administering the instant composition.

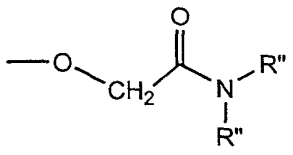
Transdermal delivery systems include patches, gels, tapes and creams, and can contain excipients such as solubilizers, permeation enhancers (e.g., fatty acids, fatty acid esters, fatty alcohols and amino acids), hydrophilic polymers (e.g., polycarbophil and polyvinylpyrolidone), and adhesives and tackifiers (e.g., polyisobutylenes, silicone-based adhesives, acrylates and polybutene).

The transdermal administration of folic acid can be facilitated by using the following ester form, which is hydrolyzed <u>in vivo</u>:



This ester can be a mono-ester (where either R or R' = H) or a di-ester (where neither R or R' is H). By way of example, R and R' can be independently selected from the following groups: lower alkyl from 1-8 carbons (e.g., methyl, ethyl, propyl and butyl); branched lower alkyl from 1-8 carbons (e.g., isopropyl, isobutyl and sec-butyl); cycloalkyl having 3-7 carbons (e.g., cyclopentyl and cyclohexyl); aryl (e.g., phenyl and substituted phenyl having 1-2 substitutients selected from lower alkyl and halo alkoxyl); and arylalkyl, where the alkyl is a straight or branched chain of 1-8 carbons, and aryl is a phenyl or substituted phenyl.

Glycolamide esters (both mono- and di-) can also be used for transdermal folic acid administration. Esters of this type are known to be useful as pro-drugs, and are cleaved rapidly in-vivo (J. Med. Chem. (1989) 32(3):727-34). In glycolamide esters, at least one of R or R' has the structure:



where (i) each R" is independently a lower alkyl (from 1-5 carbons) or, alternatively, (ii) both R" groups form an N-containing, 5-7-membered ring having 4-6 carbons.

Transmucosal delivery systems include patches, tablets, suppositories, pessaries, gels and creams, and can contain excipients such as solubilizers and enhancers (e.g., propylene glycol, bile salts and amino acids), and other vehicles (e.g., polyethylene glycol, fatty acid esters and derivatives, and hydrophilic polymers such as hydroxypropylmethylcellulose and hyaluronic acid).

Injectable drug delivery systems include solutions, suspensions, gels, microspheres and polymeric injectables, and can comprise excipients such as solubility-altering agents (e.g., ethanol, propylene glycol and sucrose) and polymers (e.g., polycaprylactones and PLGA's). Implantable systems include rods and discs, and can contain excipients such as PLGA and polycaprylactone.

Oral delivery systems include tablets and capsules. These can contain excipients such as binders (e.g., hydroxypropylmethylcellulose, polyvinyl pyrilodone, other cellulosic materials and starch), diluents (e.g., lactose and other sugars, starch, dicalcium phosphate and cellulosic materials), disintegrating agents (e.g., starch polymers and cellulosic materials) and lubricating agents (e.g., stearates and talc).

Solutions, suspensions and powders for reconstitutable delivery systems include vehicles such as suspending agents (e.g., gums, zanthans, cellulosics and sugars), humectants (e.g., sorbitol), solubilizers (e.g., ethanol, water, PEG and propylene glycol), surfactants (e.g., sodium lauryl sulfate, Spans, Tweens, and cetyl pyridine), preservatives and antioxidants (e.g., parabens, vitamins E and C, and ascorbic acid), anti-caking agents, coating agents, and chelating agents (e.g., EDTA).

Methods of determining therapeutically effective doses for administering the instant pharmaceutical composition in humans are known in the art. For example, these effective doses can readily be determined mathematically from the results of animal studies.

In one embodiment of the instant invention, the daily dose of folic acid administered to a subject according to the instant invention is from about 25 μg to about 1 g. Current recommendations in the art for daily folic acid dosages, upon which indication-specific dosages can readily be determined, include, for example: 50 μg/day (minimum effective dose, general population); 200 μg/day (recommended daily allowance, general

population); 400 µg/day (women of reproductive age); 800 µg/day (pregnant women); 500 µg/day (lactating women); 4 mg/day (women who have previously delivered a fetus having NTD); 1-5 mg/day (reduction of elevated homocysteine levels); and 200 µg/day (reduction of elevated plasma homocysteine levels in intermediate hyperhomocysteinemia patients).

The instant pharmaceutical compositions can be packaged in the form of pharmaceutical kits or packages in which the daily (or other periodic) dosages are arranged for proper sequential administration. Accordingly, this invention further provides a drug delivery system comprising a pharmaceutical package containing a plurality of dosage units, adapted for successive daily administration, each dosage unit comprising at least one of the instant pharmaceutical compositions.

This drug delivery system can be used to facilitate administering any of the various embodiments of the instant pharmaceutical compositions. In one embodiment, the system contains a plurality of dosages to be taken daily via oral administration (as commonly practiced in the oral contraceptive art). In another embodiment, the system contains a plurality of dosages to be administered weekly via transdermal administration (as commonly practiced in the hormone replacement art), thus providing continuous folic acid delivery.

For added convenience, the instant system can further comprise additional dosage units that contain folic acid, but no other active ingredient. Such delivery system could provide a total of 28 oral dosage

units, consistent with normal practice in the art of oral contraception. More specifically, an oral contraceptive delivery system could provide 21 daily dosage units, each comprising folic acid and oral contraceptive, and 7 additional dosage units comprising only folic acid and a suitable carrier. This type of system is consistent with the beneficial practice of daily, uninterrupted administration widely used with oral contraceptives.

This invention will be better understood by reference to the Examples which follow, but those skilled in the art will readily appreciate that the information detailed is only illustrative of the invention as described more fully in the claims which follow thereafter.

Example 1

Estrogen-Related Compounds

17-β-estradiol

Conjugated estrogens (including estrone sulfate, equilin, and 17-α-dihydroequilin)

Esterified estrogens

Estradiol

Estradiol valerate

Estriol

Estrone

Estrone sulfate

Estropipate

Ethinyl estradiol

Mestranol

Example 2

Selective Estrogen Receptor Modulators (SERMS)

Droloxifene

Idoxifene

Levormeloxifene

Raloxifene

Example 3

Progestin-Related Compounds

Available World-Wide

17-deacetyl norgestimate

Desogestrel

Ethynodiol diacetate

Levonorgestrel

Medroxyprogesterone acetate

Norethindrone

Norethindrone acetate

Norgestimate

Norgestrel

Progesterone

Available Outside the U.S.

3-keto desogestrel

Chlormadinone acetate

Cyproterone acetate

Dienogest

Dydrogesterone

Gestodene

Lynestrenol

Megestrol

Norethisterone

Norethisterone acetate

Norgestrienone

Quingestanol acetate

Example 4

Androgen-Related Compounds

Fluoxymesterone

Methyltestosterone

Testosterone

Testosterone enanthate

Example 5

Oral Contraceptives

Brand Name	Manufacturer**	ERC	PRC
DESOGEN	Organon	Ethinyl estradiol	Desogestrel
ORTHO CEPT	Ortho McNeil	Ethinyl estradiol	Desogestrel
DEMULEN 1/50	Searle	Ethinyl estradiol	Ethynodiol diacetate
ZOVIA 1/35	Watson	Ethinyl estradiol	Ethynodiol diacetate
DEMULEN 1/35	Searle	Ethinyl estradiol	Ethynodoil diacetate
ZOVIA 1/50	Watson	Ethinyl estradiol	Ethynodoil diacetate
LEVLEN	Berlex	Ethinyl estradiol	Levonorgestrel
TRI-LEVLEN	Berlex	Ethinyl estradiol	Levonorgestrel
LEVORA	Watson	Ethinyl estradiol	Levonorgestrel
ALESSE	Wyeth Ayerst	Ethinyl estradiol	Levonorgestrel
NORDETTE	Wyeth Ayerst	Ethinyl estradiol	Levonorgestrel
TRIPHASIL	Wyeth Ayerst	Ethinyl estradiol	Levonorgestrel
OVCON 35	Apothecon	Ethinyl estradiol	Norethindrone
OVCON 50	Apothecon	Ethinyl estradiol	Norethindrone
JENEST	Organon	Ethinyl estradiol	Norethindrone
ORTHO NOVUM 7/7/7	Ortho McNeil	Ethinyl estradiol	Norethindrone
ORTHO NOVUM 1/35	Ortho McNeil	Ethinyl estradiol	Norethindrone

Brand Name	Manufacturer	ERC	PRC
ORTHO NOVUM 1/50	Ortho McNeil	Mestranol	Norethindrone
ORTHO NOVUM 10-11	Ortho McNeil	Ethinyl estradiol	Norethindrone
NORETHIN 1/35E	Roberts	Ethinyl estradiol	Norethindrone
NORETHIN 1/50M	Roberts	Mestranol	Norethindrone
NORETHIN 1/35	Searle	Ethinyl estradiol	Norethindrone
NORETHIN 1/50	Searle	Mestranol	Norethindrone
BREVICON	Searle	Ethinyl estradiol	Norethindrone
NORINYL 1+35	Searle	Ethinyl estradiol	Norethindrone
NORINYL 1+50	Searle	Mestranol	Norethindrone
NOR-QD	Searle		Norethindrone
TRI-NORINYL	Searle	Ethinyl estradiol	Norethindrone
NELOVA 0.5/35	Warner Chilcott	Ethinyl estradiol	Norethindrone
NELOVA 1/35	Warner Chilcott	Ethinyl estradiol	Norethindrone
NELOVA 1/50	Warner Chilcott	Mestranol	Norethindrone
NELOVA 10/11	Warner Chilcott	Ethinyl estradiol	Norethindrone
NECON 0.5/35	Watson	Ethinyl estradiol	Norethindrone
NECON 1/35	Watson	Ethinyl estradiol	Norethindrone
NECON 1/50	Watson	Mestranol	Norethindrone
NECON 10/11	Watson	Ethinyl estradiol	Norethindrone
ESTROSTEP 21	Parke Davis	Ethinyl estradiol	Norethindrone acetate
ESTROSTEP Fe	Parke Davis	Ethinyl estradiol	Norethindrone acetate
LOESTRIN Fe 1.5/30	Parke Davis	Ethinyl estradiol	Norethindrone acetate

Brand Name	Manufacturer	ERC	PRC
LOESTRIN Fe 1/20	Parke Davis	Ethinyl estradiol	Norethindrone acetate
NORLESTRIN 1/50	Parke Davis	Ethinyl estradiol	Norethindrone acetate
NORLESTRIN 2.5/50	Parke Davis	Ethinyl estradiol	Norethindrone acetate
GENORA 1/35	Watson	Ethinyl estradiol	Norethisterone
GENORA 1/50	Watson	Mestranol	Norethisterone
GENORA 0.5/35	Watson	Ethinyl estradiol	Norethisterone
MICRONOR	Ortho McNeil		Norgestimate
ORTHO CYCLEN	Ortho McNeil	Ehinyl estradiol	Norgestimate
ORTHO TRI-CYCLEN	Ortho McNeil	Ethinyl estradiol	Norgestimate
LO/OVRAL	Wyeth Ayerst	Ethinyl estradiol	Norgestrel
OVRAL	Wyeth Ayerst	Ethinyl estradiol	Norgestrel
OVRETTE	Wyeth Ayerst		Norgestrel

** The manufacturers listed in this and other Examples are fully identified, by address, in Physicians' Desk Reference, 51st Ed. (1997) Medical Economics.

Example 6

Hormone Replacement Therapy
Vaginal Estrogen Preparations

Brand	ERC	Formulation
PREMARIN	Conj. Estrogens	Cream
ORTHO DIENOESTROL	Dienoestrol	Cream
OVESTIN	Estriol	Cream
ORTHO-GYNEST	Estriol	Pessary
TAMPOVAGAN	Stilbestrol	Pessary
ESTRING	Estradiol	Vaginal ring
VAGIFEM	Estradiol	Vaginal tablet

Example 7

Hormone Replacement Therapy
Transdermal Estrogen Preparations

Brand	ERC
ALORA	Estradiol
CLIMARA	Estradiol
DERMESTRIL	Estradiol
ESTRADERM	Estradiol
ESTRADERM TTS or MX	Estradiol
EVOREL	Estradiol
FEMATRIX	Estradiol
FEMPATCH	Estradiol
FEMSEVEN	Estradiol
MENOREST	Estradiol
PROGYNOVA TS	Estradiol
VIVELLE	Estradiol

Example 8

Hormone Replacement Therapy
Period-Free Therapy

Type	Brand	ERC	PRC
Continuous	CLIMESSE	Estradiol	Norethisterone
Combined therapy	EVORELCONTI	Estradiol	Norethisterone
	KLIOFEM	Estradiol	Norethisterone
	PREMIQUE	Conj. Estrogens	Medroxyprogesterone
	PREMPRO	Conj. Estrogens	Medroxyprogesterone acetate
Gonadomimetic	LIVIAL		

Example 9

Hormone Replacement Therapy
Estrogen Preparations

Brand	ERC	Formulation
ESTROGEL	Estradiol	Gel
SANDRENA	Estradiol	Gel
ESTRADIOL IMPLANT	Estradiol	Pellet implant
PREMARIN	Conjugated estrogens	Tablet
ESTRATAB	Esterified estrogens	Tablet
ESTRATEST ESTRATEST HS	Esterified estrogens Methyltestosterone	Tablet
MENEST	Esterified estrogens	Tablet
CLIMAGEST	Estradiol	Tablet
CLIMAVAL	Estradiol	Tablet
ELLESTE SOLO	Estradiol	Tablet
ESTRACE	Estradiol	Tablet
PROGYNOVA	Estradiol	Tablet
ZUMENON	Estradiol	Tablet
HORMONIN	Estradiol, estrone, estriol	Tablet
HARMOEN	Estrone	Tablet
OGEN	Estropipate	Tablet
ORTHO-EST	Estropipate	Tablet

Example 10

Combined Sequential Hormone Replacement Therapy

Type	Brand	ERC	PRC	Formul.
1/month	PREMIQUE CYCLE	Conj. Estrogens	Medroxy-progesterone	Tablet
	PREMPHASE	Conj. Estrogens	Medroxyproges-terone acetate	Tablet
	PREMPAK-C	Conj. Estrogens	Norgestrel	Tablet
	FEMPAK	Estradiol	Dydrogesterone	Tablet Patch
	FEMOSTON	Estradiol	Dydrogesterone	Tablet
	CYCLO-PROGYNOVA	Estradiol	Levonorgestrel	Tablet
	NUVELLE	Estradiol	Levonorgestrel	Tablet
	NUVELLE TS	Estradiol	Levonorgestrel	Patch
	CLIMAGEST	Estradiol	Norethisterone	Tablet
	ELLESTE DUET	Estradiol	Norethisterone	Tablet
	ESTRACOMBI	Estradiol	Norethisterone	Tablet Patches
	ESTRAPAK	Estradiol	Norethisterone	Tablet Patches
	EVOREL-PAK	Estradiol	Norethisterone	Tablet Patches
	EVORELSEQUI	Estradiol	Norethisterone	Tablet Patches
	TRISEQUENS	Estradiol, estriol	Norethisterone	Tablet
	IMPROVERA	Estrone	Medroxy-progesterone	Tablet
	MENOPHASE	Mestranol	Norethisterone	Tablet
1/qtr.	TRIDESTRA	Estradiol	Medroxy-progesterone	Tablet

Example 11

Hormone Replacement Therapy
Progestin-Only Formulations

Brand	PRC	Formulation
AMEN	Medroxyprogesterone acetate	Tablet
CYCRIN	Medroxyprogesterone acetate	Tablet
PROVERA	Medroxyprogesterone acetate	Tablet
AYGESTIN	Norethindrone acetate	Tablet

Example 12

Hormone Replacement Therapy
Androgenic Formulations

Brand Name	Manufacturer	Hormone Content
HALOTESTIN	Upjohn	Fluoxymesterone Oral
ANDROID	ICN	Methyltestosterone Oral
ORETON	ICN	Methyltestosterone Oral
TESTRED	ICN	Methyltestosterone Oral
DEPO-TESTOSTERONE	Upjohn	Testosterone cypionate Injectable
DELATESTRYL	BTG Pharmaceuticals	Testosterone enanthate Injectable
TESTODERM	Alza	Testosterone, USP Transdermal

Example 13

Formulation For Folic
Acid-Containing Oral Contraceptive

Ethinyl Estradiol (to deliver 35 µg)

Norethindrone (to deliver 1.0 mg)

Folic Acid (to deliver 400 µg)

Lactose, NF

Pregelatinized Starch, NF

Magnesium Stearate, NF

What is claimed is:

1. A pharmaceutical composition comprising (a) an oral contraceptive for preventing pregnancy in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the oral contraceptive is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

2. The pharmaceutical composition of claim 1, wherein the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

3. A pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a menopausal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

4. The pharmaceutical composition of claim 3, wherein the menopausal condition is a peri-menopausal condition.

5. The pharmaceutical composition of claim 3, wherein the menopausal condition is a post-menopausal condition.

6. The pharmaceutical composition of claim 3, wherein the disorder is selected from the group consisting of cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

7. A pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a hypogonadal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

8. The pharmaceutical composition of claim 7, wherein the subject is female, and the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

9. The pharmaceutical composition of claim 7, wherein the subject is male, and the disorder is a cardiovascular disorder.

10. A method of administering folic acid to a subject for whom an oral contraceptive is indicated for preventing pregnancy, which comprises administering to the subject the pharmaceutical composition of claim 1, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

11. The method of claim 10, wherein the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

12. A method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a menopausal condition, which comprises administering to the subject the pharmaceutical composition of claim 3, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

13. The method of claim 12, wherein the menopausal condition is a peri-menopausal condition.

14. The method of claim 12, wherein the menopausal condition is a post-menopausal condition.

15. The method of claim 12, wherein the disorder is selected from the group consisting of cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

16. A method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a hypogonadal condition, which comprises administering to the subject the pharmaceutical composition of claim 7, wherein the subject is from a population whose

members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

17. The method of claim 16, wherein the subject is female, and the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

18. The method of claim 16, wherein the subject is male, and the disorder is a cardiovascular disorder.

19. A drug delivery system comprising a pharmaceutical package containing a plurality of dosage units, adapted for successive daily administration, wherein each dosage unit comprises a pharmaceutical composition selected from the group consisting of an oral contraceptive and a hormonal replacement composition.

20. The drug delivery system of claim 19, wherein each dosage unit comprises an oral contraceptive.

FOLIC ACID-CONTAINING PHARMACEUTICAL COMPOSITIONS, AND RELATED METHODS AND DELIVERY SYSTEMS

Abstract of the Disclosure

This invention provides folic acid-containing pharmaceutical compositions comprising either an oral contraceptive or a hormone replacement composition. This invention also provides methods of administering folic acid to a subject using the instant pharmaceutical compositions. Finally, this invention provides a drug delivery system useful for administering the instant pharmaceutical compositions.

DOCKET NO. ORT986

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am an original, joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled Folic Acid-Containing Pharmaceutical Compositions, And Related Methods And Delivery Systems, the specification of which

(check one) ☐ is attached hereto.

☒ was filed on April 16, 1999 as

Application Serial No. 09/292027

and was amended on _____.
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s):

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

60/082,068 (Application Number) — April 17, 1998 (Filing Date)

(Application Number) — (Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No. — Filing Date — Status

Application Serial No. — Filing Date — Status

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith as well as to file equivalent patent applications in countries foreign to the United States including the filing of international patent applications in accordance with the Patent Cooperation Treaty: Audley A. Ciamporcero, Jr. (Reg. #26,051), Steven P. Berman (Reg. #24,772), Andrea L. Colby (Reg. #30,194), Michael Stark *(Reg. #32,495), and Alan J. Morrison (Reg. #37,399) One Johnson* & Johnson Plaza, New Brunswick, NJ 08933 and Marjorie Hunter

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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